UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

CANDICE KRUSZKA AND ALAN KRUSZKA, Plaintiffs v. NOVARTIS PHARMACEUTICALS CORP., Defendant.	Case No.: 0:07-cv-02793-DWF/JJK

NOVARTIS PHARMACEUTICALS CORPORATION'S MEMORANDUM OF LAW IN SUPPORT OF ITS *DAUBERT* MOTION TO EXCLUDE TESTIMONY OF PLAINTIFFS' EXPERT DR. ROBERT MARX

Novartis Pharmaceuticals Corporation ("Novartis") hereby moves to exclude certain testimony of plaintiffs' retained oral surgery expert witness, Robert Marx, D.D.S, because plaintiffs cannot satisfy their burden of establishing that his opinions are admissible under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and Federal Rules of Evidence 702 and 401-403. Dr. Marx is an oral surgeon who has not reviewed any dental (or medical) records of Candice Kruszka and does not present any opinions in this case that are specific to Mrs. Kruszka or her jaw problems. Instead, plaintiffs Candice and Alan Kruszka want Dr. Marx to opine about what he calls "bisphosphonate-induced osteonecrosis of the jaw" ("BIONJ"). The Plaintiffs' Steering Committee initially designated Dr. Marx to address various other topics, as set forth in his 2008 expert report, which was served on Novartis in the multidistrict litigation

("MDL") proceedings in the United States District Court for the Middle District of Tennessee ("the MDL court") on behalf of plaintiffs in other Aredia®/Zometa® lawsuits. *See* Expert Report of Dr. Robert Marx ("Marx Report") (Ex. 1); Rebuttal Report of Dr. Robert Marx ("Rebuttal Report") (Ex. 2).[1] Novartis moved to exclude various opinions of Dr. Marx in the MDL proceedings. The MDL Court denied Novartis's *Daubert* motion in part, with no analysis or elaboration, *see* Order, *In re Aredia & Zometa Prods. Liab. Litig.*, No. 3:06-MD-1760 (M.D. Tenn. Aug. 13, 2009) (MDL ECF No. 2814) (Ex. 3), but did not decide the admissibility issues presented herein.[2]

The opinions challenged here involve discrete aspects of Dr. Marx's proposed testimony that are inadmissible for the reasons set forth below.

FACTUAL STATEMENT

Zometa® and Aredia® (in the form of generic pamidronate) are intravenous bisphosphonate medications that remain on the market with approval by the Food and Drug Administration ("FDA"). Oncologists typically prescribe Zometa® or pamidronate to patients – like Mrs. Kruszka – with multiple myeloma or breast cancer that has metastasized (spread) to bone or other kinds of metastatic cancer. Oncologists use Zometa® to protect patients from cancer-related bone destruction and the potentially paralyzing and deadly consequences of such bone destruction, including pathologic fractures and spinal cord compression. Novartis markets and sells Zometa® (and has

[1] All transcript excerpts and other exhibits submitted with this motion are cited as "Ex. ___."

[2] The MDL court addressed some of Dr. Marx's generic opinions, but not as to how they relate to Mrs. Kruszka or the specific facts at issue in this case.

marketed and sold Aredia® in the past). These bisphosphonate drugs have "revolutionized treatment of bone metastases," *see, e.g.*, B. Petrut, *A Primer of Bone Metastases Management in Breast Cancer Patients,* 15 Curr. Oncol. S50, S50 (2008) (Ex. 4), and oncologists have continued to prescribe them as standard-of-care drugs even after learning about reports of osteonecrosis of the jaw ("ONJ") in bisphosphonate patients.

Dr. Marx acknowledges that Aredia® and Zometa® "have dramatically extended life, reduced skeletal complications, reduced pain, and thus improved the quality of life for individuals with metastatic bone cancer." Robert Marx, *et al., Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment,* 63 J. Oral Maxillofac Surg. 1567, 1571 (2005) (citations omitted) (Ex. 5); *see also* 5/26/09 Dep. Tr. of Dr. Robert Marx at 1391-92 ("5/26/09 Marx Dep.") (bisphosphonate drugs "[p]lay a key role in the management of cancer-related bone disease") (Ex. 6). These opinions are borne out by the literature. By preventing pathologic fractures in cancer patients, these medications necessarily can prolong life.[3] Moreover, increasing scientific evidence shows that Zometa® slows the progression of cancer, extends survival, and offers other benefits to cancer patients.[4]

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[3] *See, e.g.*, Fred Saad et al., *Pathologic Fractures Correlate with Reduced Survival in Patients with Malignant Bone Disease*, 110 Cancer 1860, 1864-1865 (2007) (Ex. 7).

[4] *See, e.g.*, Gareth Morgan et al., *First-Line Treatment with Zoledronic Acid as Compared with Clodronic Acid in Multiple Myeloma (MRC Myeloma IX): A Randomised Controlled Trial*, 376 Lancet 1989, 1989 (2010) ("overall survival improved [for patients who received zoledronic acid (Zometa®)] independently of prevention of skeletal-related events, showing that zoledronic acid has treatment benefits beyond bone health") (Ex. 8); *see also* Fred Saad, *New Research Findings on Zoledronic Acid: Survival, Pain, and*

ADMISSIBILITY STANDARDS UNDER *DAUBERT* AND RULE 702

In *Daubert*, the Supreme Court addressed the admissibility of expert testimony and established "the exacting standards of reliability such evidence must meet." *Weisgram v. Marley Co.*, 528 U.S. 440, 455 (2000). "[T]rial courts must serve as gatekeepers to ensure that proffered expert testimony is both relevant and reliable." *Wagner v. Hesston Corp.*, 450 F.3d 756, 758 (8th Cir. 2006) (internal quotation marks omitted); *see also Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 988 (8th Cir. 2001) ("In exercising its gatekeeping function, a district court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" (quoting *Daubert*, 509 U.S. at 592-93)). Plaintiffs, as the proponents of the testimony, have the burden of proving that the testimony is admissible under *Daubert* and its progeny. *See, e.g.*, *Polski v. Quigley Corp.*, 538 F.3d 836, 841 (8th Cir. 2008); *Menz v. New Holland N. Am., Inc.*, 507 F.3d 1107, 1114 (8th Cir. 2007).

First, plaintiffs must establish that the witness has the necessary expertise, in the form of "knowledge, skill, experience, training, or education," Rule 702, to render an opinion on the specific issue addressed by his proposed testimony. *See, e.g.*, *Wheeling Pittsburgh Steel Corp. v. Beelman River Terminals, Inc.*, 254 F.3d 706, 715 (8th Cir. 2001).

Second, plaintiffs must establish that the expert's testimony is "reliable" – *i.e.*, that the testimony is "ground[ed] in the methods and procedures of science," as opposed to

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Anti-tumour Effects, 34 Cancer Treat. Rev. 183, 184 (2008) (Ex. 9).

the expert's "subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 589-90 (quotation marks omitted); *see* Rule 702 (testimony must be "based upon sufficient facts or data" and "the product of reliable principles and methods" and the expert witness must have "applied the principles and methods reliably to the facts of the case"). "Failure to show the reliability of *each step* in an expert's methodology is fatal under *Daubert*." *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1042 (D. Minn. 2007), *aff'd*, 596 F.3d 884 (8th Cir. 2010) (emphasis added) (citing *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1245 (11th Cir. 2005)).

Third, plaintiff must establish that the testimony "will help the trier of fact" in understanding issues relevant to the case, Fed. R. Evid. 702, which means that the testimony must have "a valid scientific connection" to – *i.e.*, must "fit" – the pertinent inquiry in the lawsuit. *Daubert*, 509 U.S. at 591-92 ("An additional consideration under Rule 702 . . . is whether expert testimony proffered in the case is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute") (citation omitted). Expert opinions that are irrelevant and/or unfairly prejudicial and confusing under Federal Rules of Evidence 401 to 403 should also be excluded.[5]

[5] *See, e.g., In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 545 (S.D.N.Y. 2004) (allowing expert witnesses to offer what amounted to personal opinions of corporate conduct would be confusing and unfairly prejudicial because the jury might base its decisions on those ethical opinions, rather than the pertinent legal standards).

ARGUMENT

Other courts within the Eighth Circuit have issued *Daubert* rulings limiting Dr. Marx's testimony in the Aredia®/Zometa® litigation.[6] However, a district court in Louisiana excluded Dr. Marx's opinions as both a general and case-specific causation expert after concluding they were "classic ipse dixit and will be totally disregarded by the court." *Perkins v. Novartis Pharm. Corp.*, CIV.A. 12-662, 2013 WL 2949045, at *3 (W.D. La. June 14, 2013). The *Perkins* Court explained that "Dr. Marx is displaying an obvious lack of objectivity required of an expert witness in quest of the truth in a court of law." *Id.* at *4 (noting that "Dr. Marx does not find a single hallmark of BIONJ to fit his own description"). Novartis asks this Court to fulfill its gate-keeping obligations by carefully scrutinizing the proposed testimony addressed herein and concluding that plaintiffs have failed to satisfy their burdens under *Daubert* and Rules 702 and 401-403 with respect to Dr. Marx's opinions. For the reasons discussed below, the Court should preclude Dr. Marx from: (a) presenting opinions regarding dose and duration; (b) presenting opinions about certain dental evaluation and treatment measures that he claims prevent BIONJ; (c) speculating that certain patients in the Zometa® and Aredia® clinical trials had ONJ caused by bisphosphonate therapy; (d) presenting general causation opinions based on adverse event reports that he has not reviewed; (e) testifying about the

[6] *Brodie v. Novartis Pharm. Corp.*, No. 4:10-cv-00138-HEA, at 4 (E.D. Mo. Jan. 20, 2012) (granting in part motion to preclude Dr. Marx's testimony on state of mind, intent, or motives of Novartis or its employees; granting motion to exclude Dr. Marx's conclusions and criticisms about clinical trials) (Ex. 10); *Baldwin/Winter v. Novartis Pharm. Corp.*, No. 06-4049-CV-C-MJW, 2012 WL 827305, at *9 (W.D. Mo. Mar. 8, 2012) (granting in part motion to preclude Dr. Marx's testimony on design of clinical trials and whether Novartis acted in "bad faith").

biological mechanism by which bisphosphonates allegedly cause ONJ; and (f) accusing Novartis of bad faith conduct.[7]

I. DR. MARX'S DOSE AND DURATION OPINIONS ARE UNDISCLOSED, BEYOND HIS EXPERTISE, AND ARE NOT THE PRODUCT OF A RELIABLE SCIENTIFIC METHODOLOGY.

The FDA-approved label for Zometa® recommends use in 4 mg doses every three to four weeks in treating cancer patients with bone metastases. *See, e.g.*, Sept. 2004 Zometa® Label at 21 (Ex. 12). The maximum duration of Zometa® therapy is not set forth in the label and is left to the prescribing oncologist's discretion. *Id.* Plaintiffs may seek to elicit testimony from Dr. Marx suggesting that a reduced dose/duration schedule is equally as effective and that a treating oncologist's risk/benefit evaluation should change over time to allow for allegedly increased ONJ risks. The Court should bar this testimony for a variety of reasons.

First, opinions regarding **Zometa® dose and duration** are not at issue in this case because Mrs. Kruszka never received Zometa®. Rather, she received Aredia® only from June 2000 to no later than January 2002. To Novartis's knowledge, Dr. Marx has **not** offered any opinion as to an alternative dose or duration of **Aredia®** treatment.[8] Therefore, any opinions Dr. Marx may attempt to offer in this case regarding Zometa®

[7] In addition, certain other opinions have been eliminated by agreement of the parties to narrow the *Daubert* issues to be presented to this Court. Specifically, Plaintiffs recently agreed that they will not present any testimony from Dr. Marx in this case regarding: (a) the state of mind, intent, or motives of NPC or the FDA (or any current or former employees of NPC or the FDA); or (b) any criticisms of the Aredia®/Zometa® clinical trials. *See* 10/25/2013 Ltr. from Skalaban to Vecchione (Ex. 11).

[8] Novartis reserves the right to challenge such an opinion should Dr. Marx attempt to offer one.

dose and duration are irrelevant and do not fit the facts of this case.[9] In addition, any opinion on Aredia® dosing and duration (if he has one) has not been disclosed and therefore cannot be considered. For these reasons alone, this Court should exclude Dr. Marx's opinions on Zometa® dose and duration and bar Dr. Marx from offering any opinions on Aredia® dose and duration.

Second, even if the Zometa® opinions were to be considered here, Dr. Marx's expert report does not set forth opinions regarding Zometa® dosage or duration of treatment. Nevertheless, in a *de bene esse* deposition taken prior to a recent trial, Dr. Marx suggested that a monthly Zometa® dose of less than 4 mg might be efficacious and that Zometa® use should be limited to 12 doses. *See, e.g.*, Dep. Tr. of Dr. Robert Marx at 88, *Guenther v. Novartis Pharm. Corp.*, No. 6:08-CV-00456-GAP-DAB (M.D. Fla. Aug. 12, 2013) ("8/12/13 Marx *Guenther* Dep.") ("Dose modification, when I reviewed their studies I noticed there was no study that actually documented that four milligrams of Zometa was a correct dose. So again, related to any drug complication, if you reduce the dose you get less of a side effect.") (Ex. 13); *see also* Trial Tr. of Dr. Robert Marx at 215, *Chiles v. Novartis Pharm. Corp.*, No. 3:06-cv-00096-HLA-JBT (M.D. Fla. Feb. 15, 2013) ("*Chiles*") ("The 12 months is what the FDA has approved it for, and they have not approved it for longer durations . . . So there's no scientific evidence that it's beneficial

[9] Zometa® and Aredia® are not the same drug. Indeed, as discussed in this and Novartis's other concurrently filed *Daubert* motions, plaintiffs' experts consistently contend that Zometa® is a *more potent* bisphosphonate that imposes a *greater risk* of ONJ than Aredia®. Accordingly, any opinions by Dr. Marx pertaining to the dose and duration of Zometa® (even assuming their validity, which Novartis disputes) have no relevance to Mrs. Kruszka, who received only Aredia® and generic pamidronate.

for any more doses other than 12.") (Ex. 14). Dr. Marx further altered his opinion on this subject, recently opining that administering more than four doses of Zometa® constitutes overdosing. Dep. Tr. of Dr. Robert Marx at 34, *Kennedy v. Novartis Pharm. Corp.*, No. 3:07-CV-1044 (M.D. Tenn Aug. 23, 2013) ("8/23/13 Marx *Kennedy* Dep.") ("my opinion is that [patients] don't need more than four doses") (Ex. 15). Because Dr. Marx has not disclosed these oncology opinions in any expert report applicable to this case, this Court should bar Dr. Marx from testifying about them pursuant to Federal Rule of Civil Procedure 37(c). *See Bess v. Cate*, 422 F. App'x 569, 571-72 (9th Cir. 2011).

Even if these opinions were deemed disclosed (and they should not be), plaintiffs cannot meet their burden to demonstrate that he is qualified to offer them. He is not a medical doctor or an oncologist, does not prescribe Zometa® for the prevention of pathologic fractures, and appropriately defers to patients' oncologists' dosage and duration decisions regarding Zometa® administration. *See, e.g.*, 8/12/13 Marx *Guenther* Dep. at 187-88; 8/23/13 Marx *Kennedy* Dep. at 30. Dr. Marx has admitted that the treating oncologist is solely responsible for decisions about dosage and duration of treatment for that doctor's patient and that he would not "tell a patient's oncologist what dose of a particular bisphosphonate to take." *See, e.g.*, Dep. Tr. of Dr. Robert Marx at 34, *Avila v. Novartis Pharm. Corp.*, No. 3:07-CV-01071 (M.D. Tenn. Oct. 21, 2011) ("10/21/11 Marx *Avila* Dep.") (testifying he "would never attempt to substitute [his] judgment for that of a trained medical oncologist as to whether and when to prescribe an intravenous bisphosphonate drug") (Ex. 16); Dep. Tr. of Dr. Robert Marx at 325, *Avila v.*

Novartis Pharm. Corp., No. 3:07-CV-01071 (M.D. Tenn. Aug. 31, 2012) ("8/31/12 Marx *Avila* Dep.") (Ex. 17).

In *Guenther v. Novartis Pharmaceuticals Corporation*, the court agreed that Dr. Marx was unqualified to opine that "a different dose would have prevented or lessened the risk of [plaintiff's] jaw disease." Trial Tr. of Dr. Robert Marx at 10-11, *Guenther v. Novartis Pharm. Corp.*, No. 6:08-CV-456-31DAB (M.D. Fla. Sept. 13, 2013) (Ex. 18). Similarly, in *Conklin v. Novartis Pharmaceuticals Corporation*, the court excluded Dr. Marx's opinion about an alternative dosing regime for Zometa® because "[t]here is no evidence in the record that based on his own experience or education he is qualified to opine that a regimen with a decreased dosage and/or frequency of Zometa administration would efficaciously treat cancer-related bone damage." No. 9:11CV-178, 2012 WL 4127295, at *8 (E.D. Tex. Sept. 18, 2012), *appeal dismissed* (5th Cir. Jan. 10, 2013). Like the courts in *Guenther* and *Conklin*, this Court should exclude Dr. Marx's dose/duration opinions because he lacks the requisite expertise.

Moreover, Dr. Marx failed to utilize a reliable methodology in developing these opinions. Indeed, he used no methodology at all, only offering his "personal opinions" on these subjects. In analyzing whether scientific methodology is reliable, a plaintiff must establish that the expert's testimony is "ground[ed] in the methods and procedures of science," as opposed to the expert's "subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 589-90 (quotation marks omitted). Plaintiffs cannot demonstrate that Dr. Marx's speculative opinions regarding Zometa® dosing and duration meet Rule 702's "exacting standards" of reliability. *See Weisgram*, 528 U.S. at 455; *Glastetter*, 252

F.3d at 990 (requiring courts to separate "expert opinion evidence based on 'good grounds' from subjective speculation that masquerades as scientific knowledge").

Dr. Marx admits that his reduced Zometa® dosing or duration theory has never been tested:

> Q. Dr. Marx, you're not testifying, are you, that a metastatic breast cancer patient would derive the same clinical benefit from a lower dose of Zometa as compared with four milligrams; are you?
>
> A. No, I am not testifying, **it's not been studie[d] or reported, it's never been tested**.

8/12/13 Marx *Guenther* Dep. at 306 (emphasis added). Dr. Marx cannot even reliably say that a reduced Zometa® dose or duration will lower a patient's risk of ONJ *because this issue has not been studied*:

> Q. So you … cannot predict whether a dosing scheduling change will alter the risk of ONJ; can you?
>
> A. **Not until it's been studied**.

Id. at 306 (emphasis added); *id.* at 338 ("Q. So you can't say that any particular patient who took monthly Zometa at 4 milligrams and then developed ONJ would not have developed ONJ had they only received monthly Zometa at 2 milligrams instead, true? A. Assuming that you're continually taking it, true."). He even admits that he cannot say what he thinks the appropriate dose and duration of Zometa® therapy is:

> Q. [D]o you know how much Zometa is enough?
>
> A. I don't. I don't think that anybody does.

8/12/13 Marx *Guenther* Dep. at 326.

Instead, Dr. Marx admits that his dosing/duration opinions are nothing more than

unsupported "personal opinions."

> Q. Your opinion that patients with metastatic cancer would not derive any further benefit from Zometa after the fourth dose is your personal opinion. Right?
>
> A. Correct.
>
> Q. Your opinion that patients with metastatic cancer don't derive any benefit from Zometa after the fourth dose is not based on any study. Correct?
>
> A. Correct.
>
> Q. You're not aware of any research published anywhere that would state that patients with metastatic cancer do no longer benefit from Zometa therapy after the fourth dose. Right?
>
> A. That's true. You asked for my personal opinion; I gave it.

See 8/23/2013 Marx *Kennedy* Dep. at 35-36; *see also* 8/31/12 Marx *Avila* Dep. at 326 ("Q. You can't, for example, say that in any specific patient, dosing that patient with 2 milligrams of Zometa would be as effective for treating that patient as 4 milligrams of Zometa for that patient's underlying metastatic cancer, right? You would never tell that to a patient's oncologist, true? / A. I would not tell that to a patient's oncologist, no."). These admissions render his "personal opinion" inadmissible:

> It is not helpful to the finder of fact for Dr. Marx to state that a drug used to fight cancer related diseases has a particular negative side effect, and that reducing the dosage and/or frequency of that drug will reduce the occurrence of the negative side effect. Rather, Dr. Marx must also *provide some factual support* that reducing the dosage and/or frequency of that drug will not only reduce the occurrence of the negative side effect, but will also be effective at fighting cancer-related diseases. Unfortunately, **Dr. Marx offers no evidence as to the efficacy of a reduced Zometa regimen, and he does not explain from where he draws his naked conclusion regarding efficacy** – certainly, it is not in either of the articles he cites.

> Additionally, Dr. Marx does not explain what specific dosage and/or frequency schedule would achieve similar results for fighting cancer-related diseases.

Conklin, 2012 WL 4127295, at *10 (bold emphasis added). Ultimately, Dr. Marx concedes that the patient's oncologist should make these risk/benefit decisions. 8/12/13 Marx *Guenther* Dep. at 187-88; 8/23/13 Marx *Kennedy* Dep. at 30.[10]

All of these admittedly "personal opinions" regarding Zometa® dose/duration amount to nothing more than inadmissible *ipse dixit*. 8/23/13 Marx *Kennedy* Dep. at 35-36; *see, e.g.*, *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert.") This Court should exclude these opinions just as the *Guenther* and *Conklin* courts did. 9/13/13 *Guenther* Trial Tr. at 10-11 (excluding Dr. Marx's opinion that "a different dose would have prevented or lessened the risk of [plaintiff's] jaw disease," which constituted "pure speculation by an unqualified expert on undisclosed opinions" that was inadmissible); *Conklin*, 2012 WL 4127295, at *10. [11]

[10] Because Dr. Marx cannot perform the risk-benefit analysis for Zometa® administration and has not been designated as a case-specific expert regarding Mrs. Kruszka's care, his dosing/duration opinions should also be excluded as irrelevant, misleading, and confusing to the jury. Fed. R. Evid. 403, 702.

[11] Further, because Dr. Marx cannot opine regarding reduced dosing to a reasonable degree of medical certainty, his opinions are also unhelpful and should be excluded. *See, e.g.*, 8/31/12 Marx *Avila* Dep. at 327 ("Q. You'd never testify, to a reasonable degree of medical certainty in court, that the dosing regimen that an oncologist chose for a particular patient was wrong, true? A. I'd testified to that, no.") (Ex. 17); *id.* at 327 ("Q. You'd never provide any testimony to a reasonable degree of medical certainty that a patient would derive the same clinical benefit from 2 milligrams of monthly Zometa as opposed to 4 milligrams of monthly Zometa, true? / A. True.").

II. THE COURT SHOULD PRECLUDE DR. MARX FROM TESTIFYING THAT DENTAL EVALUATION AND TREATMENT MEASURES PREVENT BIONJ BECAUSE THOSE GENERAL OPINIONS DO NOT FIT THE SPECIFIC FACTS OF THIS CASE AND ARE NOT SCIENTIFICALLY RELIABLE.

Dr. Marx opines that obtaining a dental examination before starting bisphosphonate therapy and avoiding oral surgery (including tooth extractions) while on bisphosphonate drugs can prevent BIONJ. *See* Marx Report ¶¶ 52, 53, 55. The Court should exclude these opinions for the following reasons.

First, Dr. Marx's general opinions regarding preventive dental treatment measures and avoiding invasive dental procedures do not "fit" the facts of this case because there is no evidence that such measures would have made any difference in Mrs. Kruszka's outcome. *See Daubert*, 509 U.S. at 591-92 (evidence must "fit" the case and courts must ensure it is proper for task at hand). Indeed, Mrs. Kruszka had a dental examination on May 15, 2000, exactly one month before her first dose of Aredia® on June 15, 2000, during which her dentist Dr. Stephanie Nettleton identified no necessary invasive dental procedures. *See* HealthCare Record of 5/15/2000 [2819-0022-0023] (Ex. 19).

Second, Dr. Marx has no scientifically reliable basis on which to opine that dental treatment measures actually prevent bisphosphonate patients from developing ONJ. He admitted that "people are collecting data" about whether preventive measures are effective, but "the jury is still out in terms of controlled data on that issue." 5/26/09 Marx Dep. at 1367; *see also* Dep. Tr. of Dr. Robert Marx at 200-01, *Stevens v. Novartis Pharm. Corp.*, No. DV-08-100 (Mont. 4th Jud. Dist. Ct. July 23, 2009) (no articles demonstrate a decreased ONJ risk "in a patient treated with bisphosphonates who receives pretreatment

dental care") (Ex. 20). For example, a 2009 study reported that, "despite . . . dental screening measures . . . the incidence of ONJ [during 2006 through 2008] actually went up instead of going down" as compared to the 2002-2005 period when the authors did not use dental screening measures. Dep. Tr. of Dr. Robert Marx at 157-61, *In re Zometa & Aredia Litig.*, No. 278MT (N.J. Super. Ct. Law Div. Dec. 8, 2009) (discussing S. Pozzi et al.) (Ex. 21). "Although prevention and management strategies have been proposed, these strategies have not been well studied scientifically." Richard Gliklich et al., *Epidemiology of Bisphosphonate-Related Osteonecrosis of the Jaws: The Utility of a National Registry*, 67 J. Oral Maxillofac. Surg. 71, 71 (2009) (Ex. 22). Thus, Dr. Marx conceded that determining "whether any particular patient would have developed ONJ, but then didn't develop ONJ because of some sort of prebisphosphonate treatment dental exam, that's an ***unknowable situation***." 5/26/09 Marx Dep. at 1367-68 (emphasis added); *see also id*. at 1651-52 (no protocol regarding preventive dental treatment has been established showing reduction of ONJ).

Dr. Marx may believe that dental treatment measures prevent ONJ, but that speculative belief is not admissible as expert testimony. *See, e.g., Pritchard v. Dow Agro Scis.*, 705 F. Supp. 2d 471, 493 (W.D. Pa. 2010) (excluding plaintiff's expert's "proffered testimony, which is based on a speculative set of facts and without a valid scientific connection, would not be helpful to the trier of fact").

III. THE COURT SHOULD EXCLUDE DR. MARX'S SPECULATION ABOUT WHETHER CERTAIN PATIENTS IN THE AREDIA®/ZOMETA® CLINICAL TRIALS HAD BIONJ.

Plaintiffs assert that Novartis should have been aware of certain cases of ONJ that

Dr. Marx now claims – based on his post hoc review of the records – occurred during the Aredia®/Zometa® clinical trials. Novartis disputes that there was any basis for Novartis (or the independent clinical trial investigators who treated the patients enrolled in the trials) to conclude during the trials that the patients had ONJ. Those clinical trials occurred long before September 2003, when Dr. Marx's letter to the editor of the Journal of Oral and Maxillofacial Surgery provided the first case report in a peer-reviewed publication about Aredia®/Zometa® patients developing what is now known as ONJ – and what Dr. Marx acknowledged at the time was a "heretofore unrecognized and unreported" adverse event. Robert Marx, *Letters to the Editor: Pamidronate (Aredia) and Zoledronate (Zometa) Induced Avascular Necrosis of the Jaws: A Growing Epidemic*, 61 J. Oral Maxillofac. Surg. 1115, 1115 (2003) (Ex. 23). Moreover, as Novartis informed the FDA before a March 2005 FDA Oncologic Drugs Advisory Committee ("ODAC") meeting, Novartis's ***retrospective*** review of data from the Aredia®/Zometa® clinical trials (involving over 8,000 patients) identified six patients who had experienced symptoms or signs "consistent with a ***potential*** diagnosis of ONJ." ODAC Submission at 21 (emphasis added) (Ex. 24). In the ***contemporaneous*** clinical trial reports, however, the clinical trial investigators did not report any of the cases as "ONJ" (and reported four of the cases as osteomyelitis of the jaw), and the investigators concluded that none of these cases were related to Aredia® or Zometa®. *See id.* Although three of the osteomyelitis cases did not qualify for an ONJ diagnosis because exposed or necrotic bone was not noted, Novartis reported them to FDA (in advance of the March 2005 ODAC meeting) as ***potential*** ONJ cases due to "the lack of a clear case definition

for ONJ and the fact that known ONJ cases have occasionally been reported as osteomyelitis." *Id*. Osteomyelitis of the jaw is an infection of the jaw bone that can cause ONJ in patients not exposed to bisphosphonates. *See Harvey v. Novartis Pharm. Corp.*, 895 F. Supp. 2d 1206, 1212-13 (N.D. Ala. 2012) (excluding plaintiff's expert for, *inter alia*, not ruling out osteomyelitis as a potential cause of plaintiff's alleged ONJ).

After Dr. Marx was retained as an expert witness for the Aredia®/Zometa® litigation, he reviewed certain records from the clinical trials and made post hoc diagnoses that five of the six patients had ONJ caused by bisphosphonates (*i.e.*, what he calls BIONJ). *See* Rebuttal Report ¶¶ 14, 14(e), 18, 19 (conceding that Dr. Marx has no opinion regarding whether sixth patient had BIONJ). However, Dr. Marx repeatedly has asserted that exposed jaw bone lasting more than eight weeks is the "key component" of his definition of BIONJ. *See, e.g.*, 5/26/09 Marx Dep. at 1355-58. But he admitted that none of the records for these clinical trial patients whom he claims had BIONJ indicate exposed bone consistent with this definition. *Id*. at 1435 (no notation in the records that Patient 609-2023 (Rebuttal Report ¶¶ 14(a), 18(c); chart number ZA-1043066) had exposed bone for more than eight weeks); 5/26/09 Marx Dep. at 1442-46 (no evidence of exposed or necrotic bone in records of Patient 627-2382 (Rebuttal Report ¶¶ 14(b), 18(d); chart number ZA-1043888)); 5/26/09 Marx Dep. at 1455-56 (no evidence of exposed bone in records of Patient 2264-11160 (Rebuttal Report ¶¶ 14(c), 18(b); chart number ZA-1041088)); 5/26/09 Marx Dep. at 1460-61, 1463 (stating that there is no evidence regarding how long "denuded [jaw] bone" lasted in Patient M6596P/6 (Rebuttal Report ¶¶ 14(d), 18(a); chart number ZA-1039780)), and admitting that there is no scientifically

reliable way to determine whether she would have developed exposed jaw bone even if she had not been exposed to bisphosphonate therapy); 5/26/09 Marx Dep. at 1468, 1473-77 (no evidence of exposed or necrotic bone in records of Patient 0521-002 (Rebuttal Report ¶¶ 14(f), 18(e); chart number ZA-1045260)).[12]

Thus, when evaluating the records of clinical trial patients whom he claims had BIONJ, Dr. Marx abandoned the methodology that he uses outside of litigation to determine whether patients have BIONJ. He simply assumed – contrary to the evidence – that these patients had exposed bone for eight weeks, his "key component" for a BIONJ diagnosis. This inconsistency demonstrates that his opinions are not based on a reliable methodology. *See, e.g.*, *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 560 (W.D. Pa. 2003) ("The reliability of plaintiff's experts' opinions is significantly undermined by the fact that they abandon the method that they themselves have defined."), 561 (because "consistency is a hallmark of the scientific method, plaintiff's experts must be required to satisfy their own standards of reliability" (citing *Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996) ("the district court should be wary that the [expert's] method has not been faithfully applied")). Although Dr. Marx may complain that the records he reviewed do not provide enough information for him to determine whether the clinical trial patients had exposed jaw bone for more than eight weeks, any such alleged lack of data does not mean that Dr. Marx is permitted to speculate regarding that key issue. *See, e.g.*, *J.B. Hunt Transp., Inc. v. Gen. Motors Corp.*, 243 F.3d 441, 444 (8th Cir.

[12] Dr. Marx also claimed that a seventh patient from the clinical trials had BIONJ, but again admitted that the records for this patient did not show any exposed bone. *See* Rebuttal Report ¶¶ 43-44 (discussing Patient 2346-20593); 5/26/09 Marx Dep. at 1480.

2001) ("[b]ecause of the deficiencies at the core of his opinion, including his own admission concerning his inability to scientifically reconstruct the accident [due to insufficient evidence]" expert's opinion "was mere speculation and pure conjecture"); *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 467-68 (E.D. Pa. 2008) ("[T]he non-existence of good data does not allow expert witnesses to speculate or base their conclusions on inadequate supporting science.")

As shown above, Dr. Marx's "methodology has been contrived to reach a particular result," which is contrary to the *Daubert* requirement of scientific reliability, *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1293 n.7 (11th Cir. 2005); *see Bland v. Verizon Wireless, (VAW) L.L.C.*, 538 F.3d 893, 898 (8th Cir. 2008) ("Without knowledge of these data points, [expert] could not extrapolate from the existing data because, as the district court reasoned, the gap between the data identified and [expert's] proffered opinion was "simply too great an analytical gap . . . to support admissibility." (omitted internal quotation marks)); *Junk v. Terminix International Co.*, 628 F.3d 439, 448 (8th Cir. 2010) (upholding exclusion of expert's testimony because expert's "failure to follow his own general practice and his reliance on unfounded assumptions in his comparative method created 'too great an analytical gap' between his opinion and the data on which it relied"); *Blue Dane Simmental Corp. v. American Simmental Association*, 178 F.3d 1035, 1040-41 (8th Cir. 1999) (excluding expert's testimony even where expert "utilized a method of analysis typical within his field, [because] that method is not typically used to make statements regarding causation without considering all independent variables that could affect the conclusion"), and his opinions are distorted by hindsight bias, *see KSR*

Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 421 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."). Therefore, the Court should preclude Dr. Marx from testifying that patients in the Aredia®/Zometa® clinical trials had BIONJ.

IV. THE COURT SHOULD PRECLUDE DR. MARX FROM GIVING GENERAL CAUSATION TESTIMONY BASED ON ADVERSE EVENT REPORTS THAT HE HAS NEVER REVIEWED.

Dr. Marx's general causation opinion is based, in part, on adverse event ("AE") reports that were submitted to FDA or Novartis. *See* Marx Report ¶ 61; *see also* Dep. Tr. of Dr. Robert Marx at 859, *In re Aredia & Zometa Prods. Liab. Litig.*, No. 3:06-MD-1760 (M.D. Tenn. Mar. 5, 2009) ("3/5/09 Marx Dep.") (Ex. 25). Dr. Marx's reliance on AE reports is fundamentally flawed. He has no way to evaluate whether they are reliable because he has not "reviewed a single one," *id*. Therefore, he does not know how many AE reports satisfy the definition of BIONJ that he uses when evaluating his own patients. *See id*. at 864-65; 5/26/09 Marx Dep. at 1355-56. Dr. Marx cannot say how many AE reports involved problems other than what he terms BIONJ, such as osteomyelitis of the jaw. 3/5/09 Marx Dep. at 860-61. He conceded that, because he has not seen the AE reports, he has "no idea what they're referring to as osteomyelitis, or anything else," *id.* at 861, and "there's always some degree of unreliability about the information that's included" in AE reports, 5/26/09 Marx Dep. at 1581.

Moreover, even if Dr. Marx had reviewed the AE reports upon which he relies, they would not provide scientifically reliable support for his causation opinions. Courts repeatedly have held that AE reports merely present anecdotes that do not rise to the level

of scientifically reliable causation proof. *See, e.g.*, *McClain*, 401 F.3d at 1250; *Soldo*, 244 F. Supp. 2d at 568. As courts have stated, relying on anecdotal case reports to support a causation opinion "is contrary to . . . good scientific practice." *Soldo*, 244 F. Supp. 2d at 542. In fact, Dr. Marx admitted that papers based on anecdotal evidence "generally are contaminated." Trial Tr. of Dr. Robert Marx at 627, *Stevens v. Novartis Pharm. Corp.*, No. DV-08-100 (D. Mont. Oct. 14, 2009) (Ex. 26). But it is plainly inconsistent – and contrary to *Daubert*'s scientific reliability standard – for Dr. Marx to rely on anecdotal information when he thinks it supports his litigation opinions while also admitting that anecdotal information is "contaminated."

V. THE COURT SHOULD PRECLUDE DR. MARX FROM PRESENTING HIS UNRELIABLE OPINION ABOUT THE BIOLOGICAL MECHANISM BY WHICH BISPHOSPHONATE DRUGS ALLEGEDLY CAUSE ONJ.

One of the important unresolved questions is the mechanism of action by which ONJ develops in a very small percentage of bisphosphonate patients. On that issue, there are several hypotheses that have not been proven by data. *See, e.g.*, Matthew Allen, et al., *The Pathogenesis of Bisphosphonate-Related Osteonecrosis of the Jaw: So Many Hypotheses, So Few Data*, 67 J. Oral Maxillofac. Surg. 61, 61 (2009) (discussing bisphosphonate-related ONJ as a "most prominent enigma[]") (Ex. 27); Gliklich, 67 J. Oral Maxillofac. Surg. at 72 ("the primary mechanism . . . is not clear"). Despite the scientific dispute regarding the issue, Dr. Marx intends to present his unproven hypothesis on the mechanism of action of ONJ at trial. *See* Marx Report ¶¶ 17(b), 19-21. However, he lacks the particular expertise required to address this complex issue because he is not a bone biologist, endocrinologist, pharmacologist, or an expert in how

bisphosphonate drugs affect bone. *See, e.g., In re Diet Drugs Prods. Liab. Litig.*, No. MDL1203, 2000 WL 962545, at *3 (E.D. Pa. June 28, 2000) ("[A] court should 'exclude proffered expert testimony if the subject of the testimony lies outside the witness's area of expertise.'") .

By contrast, Novartis has presented real bone experts to address mechanism issues. As they explain, there is no scientifically reliable support for Dr. Marx's opinions. *See* 4/28/12 Expert Report of Prof. Graham Russell ¶¶ 24, 35-36, 42-44, 51, 59-63, 65-67, 82-83, 89-90, 134, 158, 160-61 (Ex. 28); 4/26/12 Expert Report of Dr. Theresa Guise at 6, 20 (Ex. 29).

Dr. Marx asserts that ONJ develops because bisphosphonate drugs "impair and kill" osteoclasts, leading to oversuppression of bone remodeling, which occurs in the jaw at a higher rate because jaw bones undergo more remodeling generally. *See* Marx Report ¶¶ 17(b), 19-21, 42; 5/26/09 Marx Dep. at 1375-76. But he cannot cite any human studies to support his hypothesis.

Instead, Dr. Marx cited a study which he mistakenly thought involved human cells, *see id*. at 1377, and then admitted that it was actually an *in vitro* study involving a "new" animal model consisting of cells from "15-day-old fetal mouse metatarsals," *id*. at 1419-20 (citing Ermond R. Van Beek, et al., *Bisphosphonates Suppress Bone Resorption by a Direct Effect on Early Osteoclast Precursors without Affecting the Osteoclastogenic Capacity of Osteogenic Cells: The Role of Protein Geranylgeranylation in the Action of Nitrogen-Containing Bisphosphonates on Osteoclast Precursors*, 30 Bone 64 (2002) (Ex. 30)). However, Dr. Marx properly admits that one has "to be very cautious of

extrapolating animal data." Trial Test. of Dr. Robert Marx at 1556, *Boles v. Merck & Co,. Inc.*, No. 06 Civ. 9455 (JFK) (S.D.N.Y. Aug. 21, 2009) (Ex. 31). Indeed, according to Dr. Marx, the findings from animal studies should be taken "with a grain of salt." Dep. Tr. of Dr. Robert Marx at 186-87, *Rhodes v. Novartis Pharm. Corp.*, No. 6:06-CV-01168 (M.D. Tenn. July 25, 2011) (Ex. 32). The problem for plaintiffs is that Dr. Marx has not shown that it is scientifically reliable to reach a conclusion about how Zometa® (or Aredia®) affect human cancer patients' jaw bones by extrapolating from a study in which other bisphosphonates – not Zometa® or Aredia® – were applied to 15-day-old fetal mouse cells. This is unreliable extrapolation, not scientifically sound methodology. *See Joiner*, 522 U.S. at 146 (relying on studies showing one type of cancer in mice to establish causation of another type of cancer in humans is "simply too great an analytical gap between the data and the opinion proffered").

Moreover, Dr. Marx admitted that there could be studies in the literature "that actually indicate the opposite of [his] opinion, namely, that bisphosphonates are not taken up in the jaw in any higher rate than in other bones in the body." 5/26/09 Marx Dep. at 1411-12. In fact, at least three published studies contradict Dr. Marx's mechanism theory. *See id.* at 1410-14; H. Markus Weiss, et al., *Biodistribution and Plasma Protein Binding of Zoledronic Acid*, 36 Drug Metab. Dispos. 2043, 2046 (2008) ("Teeth and jaws showed no exceptional differences in drug uptake compared with other bones.") (Exhibit 102 to 5/26/09 Marx Dep.) (Ex. 33); Frieder Bauss, et al., *Ibandronate Uptake in the Jaw is Similar to Long Bones and Vertebrae in the Rat*, 26 J. Bone Miner. Metab. 406, 408 (2008) ("current data do not support the hypothesis for a preferential uptake of

bisphosphonate in the jaw being the reason for the exclusive occurrence of osteonecrosis in that bone") (Exhibit 103 to 5/26/09 Marx Dep.) (Ex. 34); Jiunn Lin et al., *Physiological Disposition of Alendronate, a Potent Anti-Osteolytic Bisphosphonate, in Laboratory Animals*, 19 Drug Metab. Dispos. 926, 929-30 (Table 4) (1991) (reporting similar uptake of bisphosphonate drug alendronate in long bones and mandibles of rats, dogs, and monkeys) (Exhibit 101 to 5/26/09 Marx Dep.) (Ex. 35). Dr. Marx not only failed to address the published studies that undermine his mechanism hypothesis, but he admitted that he had never seen them until Novartis's counsel showed them to him during his deposition. *See* 5/26/09 Marx Dep. at 1410-14. Dr. Marx's failure to address these contrary studies casts substantial doubt on the reliability of his mechanism opinions. *See, e.g., Pritchard*, 705 F. Supp. 2d at 489 (holding that expert's opinion was "unreliable" in part because he "failed to address contrary studies which were raised by Defendants or adequately explain the differences between his opinions and the findings of those studies"). Dr. Marx should be precluded from presenting his mechanism opinions to jurors because the "courtroom is not the place for scientific guesswork," *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002) (quotation marks omitted).

VI. CONCLUSION

For the foregoing reasons, the Court should grant this motion and exclude the opinions discussed above.[13]

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Respectfully submitted,

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[13] Novartis reserves the right to present additional objections (in motions *in limine* and/or at trial) to the admissibility of Dr. Marx's testimony.